MEMORANDUM August 12, 1998

SUBJECT: Interim methodology to give estimates of potency for Cumulative Exposure Project POM inventories

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I am describing a methodology, below, that can be used to give an estimate of the carcinogenic potency of the Polycyclic Organic Matter (POM) chemical grouping modeled in the Cumulative Exposure project. The methodology takes a number of potentially carcinogenic polycyclic aromatic hydrocarbons (PAH) compounds that make up the POM inventory and assigns them comparative risk estimates. In keeping with the 1986 chemical mixtures guidelines (U.S. EPA, 1986), additivity was assumed for carcinogenic potency of these PAHs as the ability of these compounds to induce similar types of effects at the same site of action is plausible (U.S. EPA, 1993a). Addition of carcinogenic potencies of the constituent PAHs in the POM inventory yielded a potency for the inventory of 6 to 16% of that of pure benzo(a) pyrene (BaP) - an interim inhalation potency estimate of BaP itself is 2.1 x 10-3 / microgram/meter^3 (U.S. EPA 1994).

a. Adaptation of existing approaches

PAHs are formed as products of incomplete pyrolysis of organic materials and are present in considerable quantities in fossil fuel combustion processes. Between 100 and 300 different individual hydrocarbons are produced. Since only micrograms of benzo(a)pyrene (an important constituent of PAH emissions) are required to initiate tumors on mouse skin, there is great potential for increased risk of developing cancer from exposure to PAHs (Hall and Groves, 1990).

There is very marked structure activity relationship that exists within this class of compounds with, for example, benzo(e)pyrene being almost inactive while benzo(a)pyrene is a potent carcinogen. While PAHs are in chemical terms relatively inert, they are lipid

soluble and tend to accumulate in organisms. It is the metabolism of these chemicals that makes them carcinogenic but also more easily excreted (Hall and Groves, 1990)

In this methodology, three previously developed approaches were adapted to provide the maximum number of PAHs with a risk estimate. The U.S. EPA (U.S. EPA, 1993a) and California EPA (Cal EPA, 1997) have provided information on specific PAHs and their relative carcinogenic potency in relation to benzo(a)pyrene. In addition the U.S. EPA Office of Emergency and Remedial Response has sponsored a non-numeric scoring exercise to estimate the cancer potency of 144 PAHs (U.S. EPA, 1993b).

Specifically, in the provisional guidance by EPA (U.S. EPA, 1993a) 7 PAHs have potency ratios assigned to them in terms of order of magnitude similarity to the potency of BaP. In the Toxic Air Contaminant Identification List developed by California EPA, BaP ratios are assigned to 9 PAHs also listed in the Cumulative Exposure Project POM inventory (Cal EPA, 1997). The U.S. EPA (U.S. EPA, 1993b) semi-quantitative scoring system assigns PAHs to bins that do not precisely correspond to ratios to BaP reported in the EPA provisional guidance (U.S. EPA, 1993a) or to the ratios reported by California EPA (Cal EPA, 1997. PAHs are described as high, moderate, marginal, or low potencies in the EPA semi-quantitative system using BaP as the reference compound. Specifically, in the semi-quantitative scoring system PAHs are either rated high and assigned a potency comparable to BaP, moderate 1-33% of BaP, marginal <1 percent of BaP with some activity, or low as inactive (U.S. EPA, 1993b). Rodent skin tumorigenesis and other *in vivo* assays, and genotoxicity studies are the primary types of information used in the analysis as well as professional judgment and structure activity relationship information.

In this methodology, the ratios used in the U.S. EPA 1993 provisional guidance and by California EPA in their program were used to adapt the EPA non-numeric or "semi-quantitative" scoring system (U.S. EPA, 1993b) as shown in Table 1 for 26 PAHs. Even though a rating of "marginal" in the semi-quantitative scoring system is less than 1 percent of BaP by definition, that definition also includes an assignment of some activity. Therefore, for the purposes of the Cumulative Exposure Project, a ratio of 0.001 was assigned to "marginal" PAHs and is consistent with the lowest value assigned this subset of PAHs by EPA in its provisional guidance (U.S. EPA, 1993a).

Table 1. Assignment of BaP potency ratios to PAHs

EPA scoring classification of cancer potency (relative to BaP) (U.S. EPA, 1993b)	BaP ratio assignment for use in the cumulative exposure project
High	1.0
Moderate	0.1
Marginal	0.001
Low	0
no assignment	-

The EPA semi-quantitative scoring exercise used five toxicologists with expertise in the mechanisms and assessment of PAH Carcinogenicity to individually assign potency scores to each of the 144 PAHs assessed (U.S.EPA, 1993b). Following independent evaluation, the scorers met to discuss and attempt to resolve differences. Even though there was a high rate of agreement, not all PAHs had consensus potency values assigned to them. For development of a quantitative estimate for this methodology, the highest potency of at least 2 of the 5 experts was chosen as the assigned potency of that specific PAH. There are 7 PAHs with non-consensus estimates included in this methodology and identified in Table 2. The uncertainty introduced by using such non-consensus values for derivation of a potency estimate for the POM inventory is expected to be small as those 7 PAHs already had potency estimates from the other two approaches or were considered to be of either very low potency or no activity. Thus, the use of non-consensus values from the semi-quantitative scoring system in this methodology did not significantly affect the potency estimate for the POM group.

In addition, several of the PAHs in the Cumulative Exposure Project emissions inventory for POM were identified as a subgroup of chemicals rather than for just one specific PAH as was done in the EPA semi-quantitative scoring exercise (U.S. EPA, 1993b). The methylbenz(a)-anthracenes/ -chrysenes/ -triphenylenes sub-group in the POM inventory as well as the methylchrysenes subgroup, have multiple members with varying potency assignments in the EPA semi-quantitative scoring method (U.S. EPA, 1993b). The assignment of potency of these subgroups can significantly affect the

determination of the potency for the POM inventory. For the PAHs in the methylbenz(a) -anthracenes/ chrysenes/ triphenylene sub-grouping, the highest potency estimate for any of the 12 members ranked in the EPA semi-quantitative scoring system gives a potency estimate equal to that of BaP. However, if an average value for all members with assigned potency estimates (U.S. EPA, 1993b) is calculated, that potency would be a ratio of 0.1 of BaP . Further speciation of the Cumulative Exposure Project inventory is not possible at this time to determine a more precise estimate of the constituents in this sub-grouping. All PAHs listed within this subgroup in the EPA semi-quantitative scoring system have at least some activity. However, there is no way to verify if the distribution of PAHs in the subgroup is reflected by an equal distribution among those with a semi-quantitative score or whether the subgroup mainly consists of higher potency PAHs. Therefore, it is a policy decision as to what potency to assign for the sub-group. In similar A similar situation exists for the methylchrysenes subgroup where the most potent member of the group has an estimate of potency similar to BaP and the average ratio to BaP is 0.2 for all PAHs within the sub-group listed in the EPA semi-quantitative approach.

b. PAH potency assignment

In general there was good agreement in the assignment of potencies to PAHs by the 2 approaches and adaptation of the third (see Table 2). For the assignment of the potency to individual PAHs in this methodology, the following rules were applied. If the same value was assigned in at least 2 out of three of the approaches where 3 values are given, then that value was used. If there is only one available value for a PAH in any of the approaches then that value was used. Only 2 PAHs have values given for 2 of the approaches and those assignments were the same. Accordingly, order of magnitude potency assignments relative to the carcinogenic potency of BaP incorporating all three approaches are presented in Table 2.

Table 2. Potency estimates for PAHs for characterized portions of the Cumulative Exposure Project POM inventory:

PAH	U.S. EPA 1993a ratio to BaP	CAL EPA 1997 ratio to BaP	U.S. EPA 1993b score adapted to U.S. EPA 1993a ratio to BaP	% of inventory sources	CEP assigned ratio to BaP
benz(a)anthracene	0.1	0.1	0.1*	3.9	0.1
benzo(a)pyrene	1.0	1.0	1.0	2.27	1.0
benzo(b)fluoranthene	0.1	0.1	1.0	2.38	0.1
benzo(k)fluoranthene	0.01	0.1	0.1*	2.17	0.1
chrysene/triphenylene	0.001	0.01	0.001	3.65	0.001
dibenz(a,h)anthracene	1.0	0.4	1.0	0.4	1.0
indeno(1,2,3 cd)pyrene	0.1	0.1	0.1	0.36	0.1
anthracene			0.001*	2.11	0.001
benzo(ghi)perylene			0.001*	6.85	0.001
fluoranthene			0.001*	4.67	0.001
phenanthrene			0	4.60	0
pyrene			0	3.03	0
anthanthene			-	0.38	-
benzo(a) and benzo(b)fluorene			0.001*	1.42	0.001
benzacenaphthylene			-	0.9	-
benzo(e)pyrene			0.001	2.59	0.001
benzo(ghi)fluoranthene			0	1.46	0
coronene			0	4.29	0
cyclopenta(cd)pyrene			0.1	2.34	0.1
methylbenz(a)-anthracenes / -chrysenes / - triphenylenes			1.0 or 0.1	6.42	1.0 or 0.1
dimethylfluoranthenes, pyrenes			-	7.61	-
perylene			0	0.71	0
methylphenanthrenes, anthracenes			0	11.0	0
dimethylphenanthrenes, anthracenes			0	5.33	0
phenylnaphthalene			-	0.7	-
benzylnaphthalene			-	0.34	-
methylfluoranthenes, pyrenes			-	6.97	-
benzo(j)fluoranthene		0.1	0.1	0.36	0.1
methylbenzofluoranthenes, benzopyrenes, perylenes			-	0.36	-
indeno(1,2,3 cd)fluoranthene			-	1.66	-
benzo(b)triphenylene			-	0.18	-
benzo(b)chrysene			0.001	0.09	0.001
acenaphthylene			0.001*	5.04	0.001
acenaphthene			-	0.24	-
fluorene			0	0.57	0
methylchrysenes		1.0	1.0 or 0.2	2.66	1.0 or 0.2

* Assumes the highest rating by at least 2/5 reviewers (EPA 1993b)

Results

In order to make an estimate of carcinogenic potency for the Cumulative Exposure Project POM inventory, there are 2 areas where extrapolations were made for data gaps; (1) potency assumptions for PAHs with no potency estimate and (2) uncharacterized portions of the Cumulative Exposure Project POM emissions inventory. For the characterized portion of the POM inventory, approximately 20% of the emissions are for PAHs with no assignment of potency. The carcinogenic potency for these PAHs was assumed on the whole to be the same as the rest of the PAH aggregate and added into the sum of potencies for the total PAH aggregate. In addition, the characterization of the Cumulative Exposure Project emissions inventory reported in Table 2 represents only 84 % of total POM emissions in the inventory. For the purposes of this analysis, the remaining 16% of the POM emissions were also assumed to be of similar carcinogenic potency as the aggregate of PAHs presented in Table 2.

Using the PAH potency assignments including assignment of subgroups to either high or average potency estimates as a policy decision and extrapolations of potency described above, two scenarios are given below to estimate the potency for the Cumulative Exposure Project POM inventory. Extrapolations of potency for data gaps were constant in both approaches with assignment of potency to the subgroups determining differences in resulting POM potency assignment. In one scenario the potencies for the methylchrysenes and methylbenz(a) -anthracenes/-chrysenes/-triphenylenes sub-categories were assigned the highest potency of any member of the group scored in the semi-quantitative analysis (U.S. EPA, 1993b). In the other, an average potency was assigned to each sub-category based on those estimates for members with described potency scores. The distribution of PAH potency assignment, as a BaP ratio, for both scenarios is given below in Table 3. Accordingly, the estimated potency for POM in the Cumulative Exposure Project POM inventory can be estimated to be 6% and 16% of the potency of BaP based on the aggregate potency of the PAHs identified in the characterized portions of the inventory and assumptions of similar toxicity for unknown constituents.

Table 3. Assignment of BaP ratio to aggregate PAH emissions for characterized portions of the Cumulative Exposure Project POM inventory:

BaP potency ratio	Scenario 1 (highest potency within subgroups)	Scenario 2 (average potency of subgroup)
1.0	12%	3%
0.1 *	12%	21%
0.001	26%	26%
0	31%	31%
no assignment	19%	19%

*A BaP ratio of 0.2 is used for the methylchrysenes when an average score is used for the sub-group.

Conclusions

There is uncertainty in the methodology presented here for determination of carcinogenic potency for the Cumulative Exposure Project POM inventory and in all three approaches used for its basis (U.S. EPA, 1993a, 1993b, Cal EPA, 1997). The EPA semi-quantitative scoring method (U.S. EPA, 1993b) only gives a rough approximation of potency using a reference compound. Adaptation of the this approach, originally intended for approximations of range of potency, to a single BaP ratio increases uncertainty in the estimate. Secondly, the assignment of a potency value to the two emissions subgroups (methylchrysenes and methylbenz(a)/-anthracenes/-chrysenes/-triphenylenes) has a significant effect on the potency assignment for the PAH aggregate in the POM inventory. In addition, the assumptions concerning potency of PAHs without a potency estimate and assignment of values to the to uncharacterized portions of the inventory increases uncertainty.

Alternatively, only using the potency profiles for those HAPs with more certainty in their estimates - those ranked by California EPA (Cal EPA ,1997) or by the U.S. EPA provisional guidance (U.S. EPA, 1993a) - and assuming the rest of the PAHs are inactive would give a potency estimate for the aggregate that may be too low given that they have been identified as having activity in the U.S. EPA semi-quantitative scoring approach (U.S. EPA ,1993b).

The emissions inventory used in the Cumulative Exposure Project contains estimates for 36 polycyclic aromatic hydrocarbons (PAHs) that are part of the polycyclic organic matter (POM) HAP group. There are other members of the POM group and of the PAH subgroup not included in the emissions inventory that could represent a potential health hazard such as nitrated PAHs, aromatic amines, and aza-arenes (Lewtas, 1993). Specifically, there are several PAHs with emissions cited by California EPA that are not listed in the CEP emissions inventory and whose carcinogenic potency is higher than that those listed for this analysis (Cal EPA, 1997). In its the seventh annual report on carcinogens, the National Toxicology Program NTP 1994) lists 15 carcinogenic PAHs of which only 7 are listed in the Cumulative Exposure Project POM inventory. Nesnow et al., have recently reported that the *in vitro* carcinogenic potency of dibenzo[a,l]pyrene - a product of incomplete combustion of fossil fuels and a PAH found in cigarette smoke condensate, extracts of indoor air particles from smoky coal combustion, and extracts of some environmental samples - to be 4 to 12 times that of BaP (Nesnow et al., 1997). This compound is not listed in the Cumulative Exposure Project POM inventory. Finally, studies of environmental coal tar mixtures were found to induce more tumors than their BaP content alone would suggest indicating the presence of other carcinogenic components (Rodriguez et al, 1997, Culp et al., 1998).

PAHs also have the potential for interactions among mixtures found in the environment which can affect their toxicity. Individual rankings of potency between the PAHs or mixtures of PAHs is dependent on the system used, dose, and component PAHs in the mixture (Rao et al., 1991, Nesnow et al., 1985). In a recent publication Nesnow et al. have studied the potential for greater than additive and less than additive carcinogenic responses within mixtures of 5 PAHs shown to be present in the environment, and having a range of tumorigenic activities, structural features (e.g. methylated vs. non methylated, condensed vs. linear), and a diversity of routes of metabolic activation (Nesnow et al., 1998). At low doses, greater than additive responses were observed between these PAHs and at the highest doses less than additive responses observed in induction of mouse lung tumor formation. However, while interactions of PAHs were observed they were limited

in extent (50 % inhibition to 2 fold enhancement) suggesting additivity of the response of the PAHs is in general a good approximation of the response to PAH mixtures.

In addition, carcinogenic potencies for some of the PAHs may also be underestimated in the three approaches used in this methodology for potency assignment. No potencies were assigned to PAHs in excess that of BaP. Dibenzo[a,l]pyrene, 5-methylchrysene, and cyclopenta[cd] pyrene have been reported to have a greater potency than BaP in the induction of mouse lung tumors (Prahalad et al., 1997). Thus, there is also the possibility that because the inventory for POM in the Cumulative Exposure Project does not account for other important of POM or PAHs and that the potency of some of the PAHs in the inventory may be underestimated, the hazard of the POM group actually present in the ambient air may be underestimated by the Cumulative Exposure Project emissions inventory.

In conclusion, this method attempts to use available information on PAH carcinogenic potency to estimate the carcinogenic potency of the Cumulative Exposure Project inventory for POM. Although containing uncertainty, it is appropriate as an interim methodology to produce estimates of risk and may also be applicable at the screening level for identification of the potential carcinogenic risk for emissions of PAH where the identity and relative amounts of the constituent PAHs are known.

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